Physical activity in recipients of solid organ transplantation

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Publication date:
2017

Chapter 1|

General introduction

Introduction

Background

Solid organ transplantation is a life-saving intervention for people with end stage organ failure. After the first successful kidney transplantation in 1954, the first liver transplantation in 1963, the first heart transplantation in 1967, and the first (isolated) lung transplantation in 1983, major improvements have been made in outcomes, and the number that has been performed has increased. In 2014, a total of 7,741 solid organ transplants were performed in the EuroTransplant region of which 1,321 were in the Netherlands.[1] These numbers translate to 46.8 transplants per million persons in the EuroTransplant region and 46.6 transplants per million persons in the Netherlands.[1] Initially, significant improvements in short-term survival were made due to the development and evolution of immunosuppressive medication, improved organ preservation, and surgical techniques. The survival curves per era of transplantation have been running rather parallel in the past decades as indicated for liver transplant recipients in Figure 1.[2,3] Improved overall survival appears to be mainly a consequence of improved short-term survival. To further increase overall survival after transplantation, focus is shifting towards improvement of long-term outcomes. Sustaining or improving quality of life and physical functioning as well as reducing morbidity from cardiovascular diseases are the primary goals currently being addressed.

Improved physical functioning or functional recovery after transplantation is a goal that is being addressed due to the fact that functional recovery after transplantation is not as good as might be expected. Overall, very few transplant recipients have a maximal rate of oxygen consumption (VO_{2peak}) within the normal range, and this reduction in VO_{2peak} is present despite the restoration of near normal organ function after transplantation.[4] Furthermore, maximal exercise capacity is limited and the level of daily activity has shown to be reduced after transplantation.[5–7]

Reducing mortality from cardiovascular disease is indicated as an important goal in improving long-term survival. Cardiovascular diseases are currently the primary noncommunicable disease in the general population and accounts for the majority of the 63% of all deaths worldwide that are accounted for by these diseases.[8] The World Health Organization identified the six risk factors associated with noncommunicable diseases as the leading risk factors for death as being: high blood pressure, tobacco use, high blood glucose levels, overweight or obesity, high cholesterol levels, and inactivity. These factors collectively contribute to a large proportion (~42%) of the deaths from cardiovascular disease.[9]

Within the renal transplant population, the incidence of cardiovascular diseases is reported to be three to five times higher when compared to age-matched controls.[10,11] Although most studies have been performed in renal transplant populations, there are indications that the increased risk is present in the other transplant populations as well.[12,13] It is likely that these life-style related secondary diseases that are of influence on cardiovascular disease are of major importance to the long-term survival in the transplant population.[14–17] The prevalence of noncommunicable diseases caused by the earlier mentioned life-style related factors is likely further increased in the transplant population with the use of immunosuppressive medication. For instance, the use of corticosteroids is associated with muscle myopathy, and the use of calcineurin inhibitors has affected mitochondrial respiration and muscle degeneration in animal models.[18,19] The use of immunosuppressive medication is thereby associated with a prolonged reduced exercise capacity after transplantation and inactivity. However, as this medication is required to prevent the rejection of the new organ, all other resources to prevent the noncommunicable diseases and its negative effects on survival should be addressed.

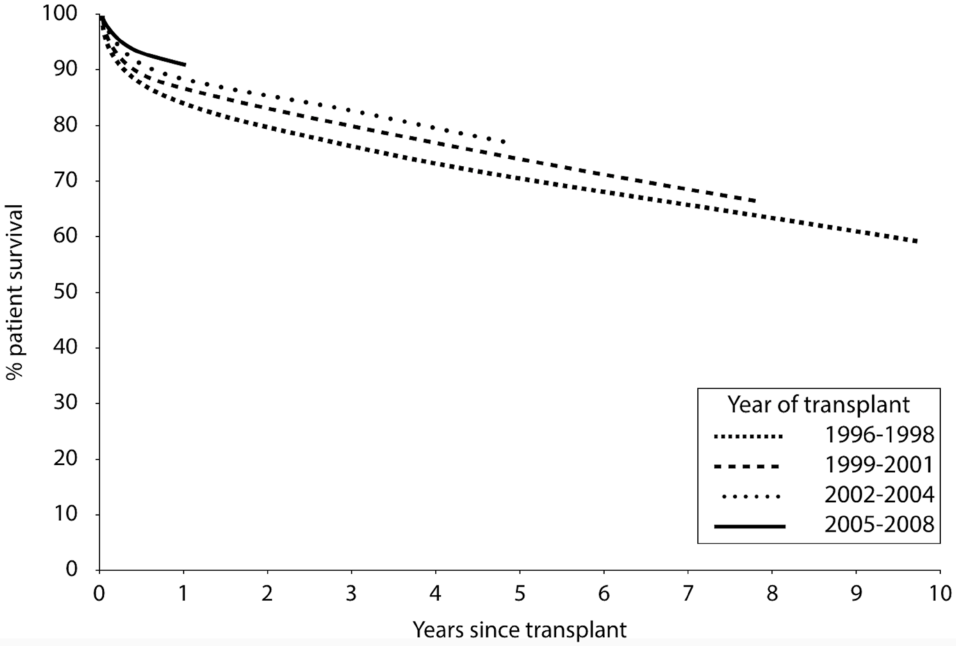

Figure 1. Long term patient survival after first elective liver transplantation in adults (DBD donors) per transplant period. Figure based on Watson CJE and Dark JH, original copyright 2012.[2]

Inactivity

Most of the noncommunicable diseases in the general population are (partly) preventable though interventions directed at a healthy lifestyle.[8] Physical inactivity is an important contributor to the development of noncommunicable diseases[20] and is reported to be the fourth leading cause of death worldwide.[21] With the elimination of physical inactivity, the life expectancy of the world's population might be expected to increase with 0.68 years, which is comparable to the elimination of the risk factors of smoking and obesity.[22]

It is suggested that 31% of the general population does not meet the minimum recommended amount of physical activity.[23] Although the number of studies performed in the transplant population is limited, the general impression is that the majority of these recipients also do not meet the recommended amount and type of physical activity. A more sedentary and inactive lifestyle is reported when compared to the general population.[6,24–30] Whether there are differences in activity levels between the several organ transplant groups is difficult to assess because no studies have been performed in which all groups of solid organ transplantation are assessed at the same time with the same instrument.

As indicated, the elimination of inactivity in the general population by increasing physical activity levels and exercise and reducing sedentary time could result in substantial health improvements and decreased mortality.[22] A sufficient amount of physical activity in the general population is associated with a reduction in all-cause mortality, coronary heart disease, high blood pressure, stroke, metabolic syndrome, type 2 diabetes, breast cancer, colon cancer, depression, and falling.[22,31] There is also strong evidence for physical activity resulting in increased cardiorespiratory and muscular fitness, a healthier body mass and composition, improved bone health, increased functional health, and improved cognitive function.[22] In the transplant population, the level of physical activity is, furthermore, positively associated to the capacity to perform activities of daily life[32], the experienced quality of life[33–36], and survival.[37–39]

Definitions and guidelines on physical activity and exercise

In order to further discuss the role of physical activity and exercise in improving health, it is important to clarify definitions of these terms. Physical activity and exercise are different concepts but are often used interchangeably or confused with each other [40] while, already in 1985, distinct definitions were introduced to distinguish them. Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure'.[40] Physical activity in daily life concerns all physical activities during the day and can be categorized into occupational, sports, conditioning, household, and other activities. Exercise, in its turn, is defined as 'a subset of physical activity that is planned, structured and repetitive and has a final or intermediate objective to improve or maintain physical fitness'.[40]

The amount of physical activity to promote or maintain health for adults is indicated in national and international guidelines. The recommendations from the American College of Sports Medicine and the American Heart Association[41], which are also used in the Netherlands as the Dutch Norm for Health-enhancing Physical Activity[42] (Nederlandse Norm Gezond Bewegen), are presented in Box 1.

Factors associated with inactivity of transplant recipients

As previously stated, the reported levels of physical activity after transplantation are limited. It is not fully clear why solid organ transplant recipients do not regain normal levels of exercise and functional capacity as physical activity is determined by many individual and environmental factors. Several physical factors specific to transplantation are likely to be associated with the decreased physical activity levels. From a behavioral perspective, recipients are expected to experience several barriers to and facilitators of physical activity which are primarily unexplored in this population.

Box 1. Guidelines on physical activity to promote or maintain health in adults:

Aerobic activities

- 30 minutes or more of moderate-intensity physical activity on at least five days a week (150 min./week). This is also referred to as the Dutch Norm for Health-enhancing Physical Activity. For adults, (18-55) physical activity is moderate-intense when a metabolic equivalent task (MET) between 4.0 and 6.5 MET is reached (think of brisk walking [5 km/h] or cycling at a pace of 16 km/h). For the elderly (>55 years), activities between 3.0 and 5.0 MET (walking 4km/h, cycling 10 km/h) are indicted as moderate-intense. Activities should be performed in bouts of at least ten minutes.
  OR
- 20 minutes or more of vigorous-intensity exercise on at least three days a week (75 min./week). This is also referred to as the Fitnorm. Performed in bouts of at least ten minutes.
  OR
- a combination of moderate-intensity and vigorous-intensity physical activity to meet this criteria.

AND

Muscle strengthening activities

- muscle strength and endurance activities of major muscle groups are recommended on two or more non-consecutive days per week. It is recommended to perform eight to ten exercises with eight to 12 repetitions for each exercise.

As indicated, reduced exercise capacity is determined across organ transplantation groups despite restoration of a nearly normal organ function of the initially failing organ after transplantation.[4] Functional recovery, therefore, lags behind that which would be expected for the organ function. Exercise capacity in this population is already affected in the pre-transplantation phase by the direct effect of the failing organ (i.e., cardiopulmonary limitations in end-stage lung disease) and secondary effects of the disease (i.e., anemia in chronic kidney disease).[4] These exercise limitations are aggravated by disuse and nutritional depletion in the end-stage disease phase leading to a catabolic state with deconditioning and muscle weakness. After transplantation, the recipients exercise tolerance is further influenced by the extended hospital and intensive care stay, prolonged sedentary time, episodes of rejection, and the use of immunosuppressive medication.[43,44] The use of immunosuppressants is associated with muscle myopathy,[18,45,46] and the use of calcineurin inhibitors has been shown to affect mitochondrial respiration and muscle degeneration.[47] Furthermore, corticosteroids can induce weight gain and osteoporosis which can subsequently limit exercise performance. Mycophenolate mofetil, azathioprine, and sirolimus can lead to bone-marrow suppression causing anemia and fatigue.[48] A study in lung transplant recipients indicated that the occurrence of an early and pathologic lactate threshold and peripheral muscle weakness contributed to the limitation of maximal exercise capacity.[49] As a result of the higher sedentary time and periods of immobilization, a muscle fiber type change is seen after transplantation, especially after lung transplantation. A shift occurs from Type I (oxidative, fatigue resistant) to Type II fibers (glycolytic, fatiguable) resulting in reduced muscle oxidative functioning and elevated blood lactate during exercise.[50,51] The peripheral muscle dysfunction pre- and post-transplantation appear to be the primary factor accountable for the impaired aerobic capacity that is demonstrated pre-operatively and post transplantation when compared to age-matched normative values.[4]

Besides the (patho)physiological barriers to physical activity, several other barriers to and facilitators of physical activity are likely to play a role in the physical activity level of the transplant population. Barriers refer to perceived obstacles that hinder the performance of physical activity, and facilitators refer to factors increasing the likelihood of performing physical activity.[52] Diverse barriers to and facilitators of physical activity have been indicated in end-stage kidney, liver, lung, and heart disease, however, only limited studies have been performed on this issue in transplant recipients. Insight into these issues within the transplant population could provide insight into key elements needing to be addressed in intervention development.

Interventions or intervention development

Increasing participation in activities of daily life might be beneficial for improving exercise capacity and reducing the risk of developing noncommunicable diseases and negative side effects of immunosuppressive medication.[44] A meta-analysis on the effects of exercise training in solid organ transplant recipients indicated that exercise training is promising but still not proven to be effective in reducing cardiovascular risk factors.[53] The available studies are limited in number, the number of participants included, and follow up.[53] Furthermore, the reported outcome measures are inconsistent and are often surrogate outcomes; studies report on exercise capacity and cardiopulmonary parameters but do not report on cardiovascular related events, graft survival, and cardiovascular and all-cause mortality.[53] The most optimal type of rehabilitation and its key components are also not yet identified. Thus far, it is also not clear if a different approach to rehabilitation is required for recipients with the different organ types that are received. The recommendations after transplantation currently differ per organ group. Where rehabilitation after heart transplantation is considered as standard care[54], this is not the case for the other solid organ transplantation groups. Clinical experience and the performance of transplant recipients at, for instance, the World Transplant Games demonstrates that the range of physical performance after transplantation is very wide.[55] The question is raised on why one recipient can be or is physically active while another is not. Understanding why recipients are physically active or inactive and the identification of associated factors of physical activity can contribute to the development of interventions.

As stated in a recent expert meeting report on exercise for recipients of a solid organ transplantation, exercise and physical activity after transplantation are an element of a long-term commitment that may lead to sustained improvements in physical functioning, quality of life, and potentially improved survival.[43] In this aspect, physical activity and exercise can potentially contribute to improving long-term outcomes and healthy aging after transplantation.

Aims and outline of this thesis

As indicated, there is promising but minimal evidence on the benefits of physical activity in recipients of solid organ transplantation. Additionally, the amount of knowledge on the physical activity level of this population is limited. Associated factors of the level of physical activity and the barriers to and facilitators of it are largely unexplored in this specific population. This thesis aims to increase the knowledge on the physical activity level in recipients of solid organ transplantation, the barriers to and facilitators of it, and the determinants and/or correlates of it after transplantation. An overview of associated factors of physical activity being addressed is schematically provided in Figure 1. The indication of barriers to and facilitators of it and the determinants and/or correlates can be used in intervention development to target the level of physical activity after solid organ transplantation.

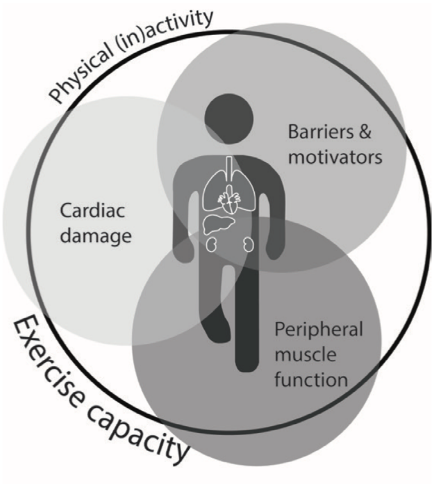

Figure 1. Schematic representation of associated factors of physical activity in recipients of kidney, liver, lung, and heart transplantation.

In an earlier study[28], it was shown that there is an association between lower levels of physical activity and increased mortality in kidney transplant recipients. However, as previously indicated, the incidence of cardiovascular disease is three to five times higher in kidney transplant recipients, and cardiac dysfunction and heart failure are highly prevalent. This potentially limits the ability to be physically active, and cardiac dysfunction, therefore, could potentially influence the indicated association between physical activity and mortality. **Chapter 2** is aimed to further investigate the relationship and to study the possible interference of cardiac function in the association between physical activity and mortality.

Where a number of studies have been performed into the associated factors of exercise capacity after solid organ transplantation, these studies all focused on maximal exercise capacity. It is expected that similar physiological processes underlie exercise limitations in submaximal or functional exercise, however, it is not clear to what extent. Furthermore, the knowledge regarding the course of submaximal exercise capacity in lung transplant recipients is restricted. In **Chapter 3,** we aimed to analyze the longitudinal development of submaximal exercise capacity in recipients of lung transplantation and explore the factors that predict this development. Results of this study can provide insight into intervention targets and timing of interventions in order to increase functional exercise capacity in recipients of lung transplantation.

To obtain additional knowledge on why someone is or is not physically active after transplantation, the qualitative study described in **Chapter 4** is aimed at generating understanding of the experienced barriers to and facilitators of physical activity in recipients of solid organ transplantation.

Chapter 5 is aimed at studying the potential underlying dimensions of a questionnaire into the barriers to and facilitators of physical activity in solid organ transplant recipients. The identification of different dimensions can potentially facilitate the application of the questionnaire in research and the utilization in intervention development in clinical settings.

The majority of previous studies into the physical activity level in solid organ transplant recipients suffer from a limited sample size and are focused on a specific group of recipients. The use of different assessment methods makes comparability between studies and between organ transplantation groups difficult. The study described in **Chapter 6** is aimed at identifying the number of recipients fulfilling the physical activity guidelines and the level of physical activity and sedentary time in a substantial number of recipients out of several groups of individuals who have received solid organ transplantation. Furthermore, the associated factors of the time spent on moderate to vigorous physical activity and sedentary time are studied. The barrier and facilitator components derived from the questionnaire described in Chapter 6 are employed in this study.

The clinical experience and results from previous studies on physical activity levels after transplantation shows us that the average level of physical activity after transplantation is limited but also that there is a wide variety in physical performance. The aim of the study described in **Chapter 7** is to study the tolerance to strenuous physical activity in recipients adhering to a healthy lifestyle. An expedition to Mount Kilimanjaro was used to study the response and tolerance to strenuous physical activity of recipients of various types of organ transplantation.

Finally, the general discussion of the primary findings of all of the chapters taken together is described in **Chapter 8** where methodological considerations and future directions for healthcare and research are also discussed.

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